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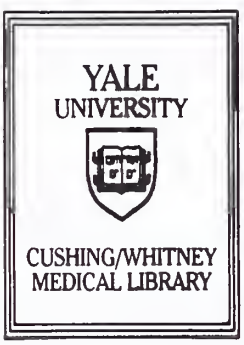
A TRANSCRANIAL DOPPLER STUDY COMPARING CEREBROVASCULAR REACTIVITY IN PATIENTS WITH ACUTE STROKE AND TRANSIENT ISCHEMIC ATTACK

Norman Whitmire, Jr.

YALE UNIVERSITY
SCHOOL OF MEDICINE

1995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A TRANSCRANIAL DOPPLER STUDY COMPARING CEREBROVASCULAR REACTIVITY IN PATIENTS WITH ACUTE STROKE AND TRANSIENT ISCHEMIC ATTACK

A Thesis Submitted
to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements
for the Degree of
Doctor of Medicine

by
Norman Whitmire, Jr.
1995

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Abstract

A TRANSCRANIAL DOPPLER STUDY COMPARING CEREBROVASCULAR REACTIVITY IN PATIENTS WITH ACUTE STROKE AND TRANSIENT ISCHEMIC ATTACK.

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The autoregulatory capacity of the brain is important to the maintenance of adequate perfusion in the face of changes in blood pressure or blood oxygen concentration. Disruptions of the cerebral vasculature, such as that seen in stroke and transient ischemic attack (TIA) can create disruption of that autoregulatory capacity. An understanding of the mechanisms and characteristics of cerebral autoregulation may help guide the management of acute stroke patients and may help in the prevention of stroke in patients with transient ischemic attack.

Twenty-six patients were studied using transcranial Doppler ultrasound. Each was given 1 gram of intravenous acetazolamide (Diamox) and monitored for 30 minutes in order to quantify the cerebrovascular reactivity, which could be inferred from the increase in blood velocity on TCD.

The stroke patients had significantly lower reactivity on the affected side than did the TIA patients on the same side ($p = 0.02$). Non-lacunar strokes demonstrated significantly lower reactivity than did lacunar strokes ($p = 0.02$). Patients with superficial (cortical) lesions showed significantly lower reactivity than did those with deep (subcortical) lesions ($p = 0.05$). The stroke patients, those with non-lacunar strokes, and those with superficial lesions demonstrated

significantly lower reactivities ($p < 0.01$ for all three groups), compared to normal subjects.

Reactivity testing in cerebrovascular disease may be useful in guiding acute management and in screening for stroke.

1. Introduction & Literature Review

1.1 Introduction

The brain is absolutely vital to the independent survival of all human beings. Its proper functioning depends on an adequate supply of oxygen and glucose. Despite being only 2% of body weight, the brain receives 15% of the total blood supply (Vander et al., 1985). There are very tight controls on the cerebrovascular system in order to insure that adequate oxygen will be able to meet the metabolic needs of the brain at any given time, for a wide range of blood pressures. The controls are mediated through vascular innervation that also responds to a number of endogenous vasodilating and vasoconstricting substances.

Disruption of the cerebral vasculature causes dysfunction of this control mechanism. Atherosclerosis, microvascular changes, like those seen in diabetes, or vascular defects, such as arteriovenous malformations can affect these vessels' ability to respond to the appropriate endogenous stimuli. In addition, occlusive processes, such as a thrombus or an embolus can create a state where vessels are maximally stimulated and are unable to respond appropriately to blood pressure changes.

Altered cerebral hemodynamics is an important factor in the pathophysiology of ischemic diseases of the brain (e.g., transient ischemic attack and stroke). It affects the cerebrovascular response to blood pressure changes and, thus, the capability of adequate brain perfusion. Techniques, such as those that measure cerebrovascular reactivity, can test the reserve capacity of brain vasculature and provide an idea of how well these blood vessels can autoregulate cerebral blood flow, especially in the setting of ischemic brain disease. These techniques involve the exogenous administration of physiologic substances, like carbon

dioxide, or drugs (e.g., acetazolamide) which increase the serum concentration of carbon dioxide. Changes in autoregulatory capacity are easily identified.

Careful monitoring of reactivity may be useful in guiding the therapy and management of some stroke patients. Patients in whom reactivity—therefore, autoregulation—is impaired may require more careful blood pressure control to insure maximal brain perfusion. However, as the vasomotor reserve capacity improves, such tight controls can become more liberal, as the brain vasculature will be better able to deal with blood pressure changes.

This thesis is a description of research using transcranial Doppler ultrasound that focuses on changes in cerebrovascular reactivity of patients immediately following a stroke or transient ischemic attack. Comparisons were made between patients with stroke and TIAs, and between the locations of the brain lesions. In Chapter 1 of this thesis, some of the previous literature concerning autoregulation, transcranial Doppler ultrasound, and cerebrovascular reactivity will be reviewed; this will set the context for the study here. Chapter 2 will describe the methods used to conduct this research. The results will be presented in Chapter 3; a number of tables and graphs have been provided to facilitate understanding of the findings. Finally, Chapter 4 will be a forum for discussion of those results and will provide suggestions for future investigations.

1.2 Autoregulation

Autoregulation is the physiological regulatory mechanism that maintains a constant flow over wide ranges of arterial blood or perfusion pressure. In the brain, this can be defined as "the occurrence of vasodilatation in response to a decrease in cerebral perfusion pressure and the occurrence of vasoconstriction in response to increased cerebral perfusion pressure" (Paulson et al., 1990). Autoregulation is dependent on cerebrovascular tone, and demonstrates an

inverse relationship between the rate of regulation and $PaCO_2$ (Aaslid et al., 1989).

Mechanisms of Autoregulation

Paulson et al., 1990 cite four mechanisms of cerebrovascular autoregulation described in the literature: myogenic, metabolic, perivascular nerves, and endothelial cell-related factors. The first mechanism is the *myogenic* which suggests that smooth muscle of the cerebral blood vessels responds to changes in transmural pressure. The small arteries then constrict or dilate in responses to increases or decreases in the pressure, respectively. This is facilitated by a change in the state of actin and myosin filaments in smooth muscle cells.

The second mechanism, the *metabolic* mechanism suggests that CO_2, H^+, O_2, adenosine, adenine, K^+ and Ca^{2+} may serve as mediators in the coupling of neuronal activity and blood flow. The exact mechanism of this is not known, however. In addition, the renin-angiotensin system may play a key role in this by controlling vasoconstriction (Paulson and Waldemar, 1991).

The third mechanism cited is regulation by perivascular nerves. Nerve fibers which originate from cranial ganglia provide autonomic motor and sensory input to cerebral blood vessels. At rest the autonomic system has little influence on cerebral blood flow; autoregulation is maintained by the smaller resistance vessels. However, when activated by endogenous (e.g. ischemia) or exogenous (e.g. CO_2 and acetazolamide) factors, the upper limits of autoregulation may be shifted to higher pressures. Conversely, acute denervation may shift the limits of autoregulation toward lower pressures; chronic stimulation may not have any effect.

The fourth mechanism cited by Paulson et al. (1990) involves factors released from endothelial cells. They point out that endothelium-derived relaxing factor

(EDRF) may be released from a blood vessel in response to higher blood flow within that vessel, causing a vasodilation.

The process of autoregulation is a complex one. Many systems are involved in its proper functioning. Understanding of how it works can guide therapy and management in situations where autoregulation is compromised or lost.

1.3 Cerebrovascular Reactivity

1.3.1 General

Carbon dioxide (CO_2) is the normal physiological modulator of cerebral blood flow (CBF) and plays a key role in an exquisite control mechanism. Increases in arterial blood CO_2 tension cause marked vasodilation. In addition, it changes arteriolar resistance by altering the pH in perivascular and intracellular vascular smooth muscle. This is possible because CO_2 can diffuse into the smooth muscle from brain tissue and from the vessels; hydrogen ions, on the other hand, are prevented from reaching vascular smooth muscle because of the blood-brain barrier. This results in an inverse relationship between cerebral blood vessel diameter and pH. (Berne and Levy, 1986)

It can be administered exogenously in order to induce vascular changes associated with hyper- and hypocapnia. The ratio of percent change in CBF plotted against the change in pCO_2 is defined as *reactivity* (DeWitt et al., 1993). The figure below is an example of a CO_2-reactivity plot (adapted from Ringelstein and Otis, 1992):

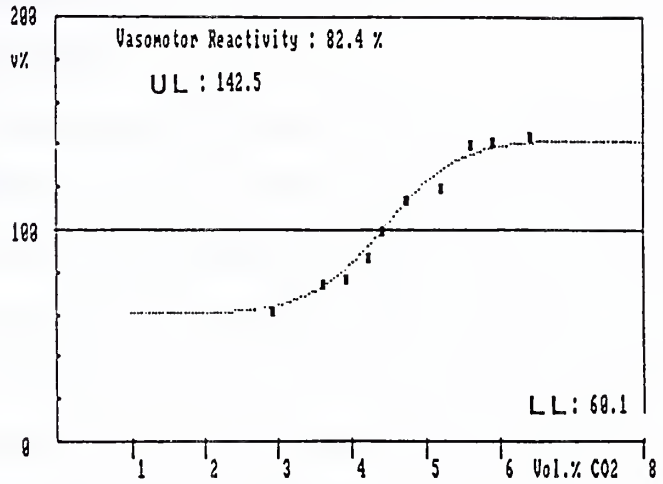

Figure 1-1. Normal vasomotor reactivity using CO_2. The *x*-axis represents the volume of gas used; the *y*-axis represents the percent change in velocity from baseline (100%).

Changes in CBF can be measured by a variety of means, including single-photon emission computed tomography (SPECT), positron-emission tomography (PET), and transcranial Doppler ultrasound (TCD) (Rogg et al., 1989). In the normal patient, hypercapnia should cause an increase in CBF detectable by PET or SPECT, and a velocity increase by TCD. A marked decrease in MCA response to hypercapnia (e.g. in the setting of carotid artery occlusion), suggests a compensatory vasodilation of vessels distal to the ICA (Bishop et al., 1986), as a consequence of these resistance vessels being maximally dilated (Ringelstein and Otis, 1992).

1.3.2 Acetazolamide in Vasomotor Reactivity

Although CO_2 is one of the physiologic substances that induces cerebral vasodilation, acetazolamide (Diamox) produces a similar effect. Acetazolamide is an inhibitor of carbonic-anhydrase, the enzyme which facilitates the conversion of CO_2 to HCO_3^- in the proximal tubule of the kidney and in erythrocytes (Sorteberg et al., 1989; Warnock, 1989). Inhibition of this enzyme

results in an increase in the blood concentration of CO_2 and mimics the effects of direct CO_2 administration.

The use of acetazolamide has been shown to be as accurate a method of inducing vasodilation as CO_2 in testing cerebrovascular reactivity (Piepgras et al., 1990; Ringelstein et al., 1992; Sorteberg et al., 1989). It creates a physiologic state that correlates to the direct inhalation of CO_2; however, at least 1 gram of the drug must be used to equal the same response (Hague et al., 1983; Ringelstein et al., 1992; Vorstrup et al., 1984). The advantages of using acetazolamide are that it is easy to administer, is independent of patients cooperation, and less uncomfortable to the patient. The disadvantage is that it induces only a vasodilatory response, so the vasoconstrictive capacity of vessels cannot be evaluated (Ringelstein et al., 1992).

1.4 Transcranial Doppler Ultrasound

1.4.1 General Principles (Aaslid, 1992; Brass et al., 1989; Caplan et al., 1990; Tegeler and Eicke, 1993)

The Doppler Principle

Christian A. Doppler (1803-1853), an Austrian physicist, described a wave principle concerning the relationship between the velocity of moving objects and the resulting frequencies of the reflected signal. This is given by the formula:

$$f = f_2 - f_0 = 2 \bullet f_0 \bullet \frac{V}{c}$$

(f = Doppler shift; f_2 = resultant frequency; f_0 = incident frequency; V = velocity of object; c = speed of sound)

Basics of Diagnostic Ultrasound

Diagnostic ultrasound takes advantage of this principle by emitting a sound wave from a transducer at 1 to 20 MHz. A moving erythrocyte shifts the

frequency in proportion to the velocity. If blood is moving toward the transducer, the wave is shortened; conversely, if the blood cell is moving away from the transducer, the wave is lengthened. The measured velocity is a component of the velocity along the line of insonation and is proportional to the cosine of the angle of insonation (ϕ) by the transducer. Blood flow moving directly toward the transducer is measured at 1.00 times the real velocity; blood traveling toward the transducer where $\phi = 60°$ will be measured at 0.5 times the velocity; and blood moving at an angle of 90° to the transducer will measure a velocity of zero. Thus, the resultant formula for flow velocity, corrected for ϕ is:

$$V = \frac{c}{2 \bullet \cos\phi} \bullet \frac{f}{f_0}$$

Transcranial Doppler Ultrasound (TCD)

Early Doppler ultrasound devices utilized continuous sound waves pulsed at 2 to 10 MHz. This technique encountered limitations when attempting to penetrate the skull, because of impaired impedance coupling[1] due to the density of bone. Aaslid et al., 1982 discovered the technique of using shorter frequency (1-2 MHz) pulsed waves which penetrate the skull better. That led to the development of transcranial Doppler (TCD) ultrasound.

Intracranial arteries can be sonated through a number of "windows" located at the temporal, occipital, and frontal bones. These correlate with the three approaches used in transcranial investigation: the transtemporal (temporal squama), transorbital (orbit), and the suboccipital/transnuchal (foramen

[1]Impedance coupling is the phenomenon that occurs when sound waves traveling through one medium encounter a different medium. For example, sound traveling through the ocean will be heard underwater, but not in the air above; similarly, the reverse is true with regard to sound traveling through air.

magnum). The arteries that can be insonated through each approach are given below (adapted from von Reutern and von Büdingen, 1993):

transtemporal-	middle cerebral terminal segment of the internal carotid anterior cerebral (A1 segment) anterior communicating posterior cerebral (P1 and P2 segments) posterior communicating superior cerebellar
transorbital-	ophthalmic internal carotid siphon anterior cerebral
suboccipital-	vertebral (intracranial portions) posterior inferior cerebellar basilar

Identification of Blood Vessels

Individual intracranial blood vessels can be located using four parameters: adjustment of the angle of insonation, depth of insonation, comparison of the shape of the wave-form, and the direction of blood flow[2].

Normal Parameters in Identifying the MCA

The middle cerebral artery (MCA) can be easily identified via the transtemporal window. The transducer should be placed immediately superior to the zygomatic arch and directed perpendicular to the bone. The MCA is found at a depth between 35-60 mm with direction of flow moving *toward* the transducer. Mean velocities range from 41 to 70 cm/sec and decreases inversely with age; however, low hematocrit levels may result in velocity increases.

[2]Above the baseline = toward the transducer; below the baseline = away from the transducer

Resistance should be low with PI of approximately 0.90 ± 25. (Brass et al., 1988; DeWitt et al., 1993)

1.4.2 Clinical Uses of TCD

Transcranial Doppler ultrasound is a useful technique in evaluating conditions affecting the cerebrovascular system, and it is commonly used in a wide variety of settings. The major uses of TCD include the following (adapted from AAN, 1990):

- detection of severe stenosis (>65%) in the major basal intracranial arteries
- assessment of the patterns and extent of collateral circulation in patients with known regions of severe stenosis or occlusion
- evaluation and following of patients with vasoconstriction of any cause, especially after subarachnoid hemorrhage (SAH)
- detection of arteriovenous malformations (AVMs) and the study of their supplying arteries and flow patterns
- assessment of patients with suspected brain death

Other Possible Uses of TCD

Table 1-1 below lists a number of other situations/disorders where TCD may be useful:

Disease	Reference
AVM	Lindegaard et al., 1986
brain death	Bode et al., 1988 Dernbach, 1989 Newell et al., 1989
brain function	Harders et al., 1989
dementia	Foerstl et al., 1989

migraine	Giller et al., 1990 Thie et al., 1990 Thie et al., 1990
normal pressure hydrocephalus	Fritz et al., 1989
pediatrics	Bode and Harders, 1989 Bode and Eden, 1989 Chadduck et al., 1991
post-partem	Bogousslavsky et al., 1989
Shy-Drager syndrome	Briebach et al., 1989
sickle cell disease	Adams et al., 1988 Brass et al., 1991
surgery	Awad and Little, 1991 Bass et al., 1989 Benichou et al., 1991 Bernstein, 1990 Brass, 1990 Padayachee et al., 1987

Table 1-1. Other possible situations using TCD. These uses have not been officially established.

1.4.3 Use of TCD in Reactivity Testing

Use in Ischemic Disease

Measurement of cerebrovascular reactivity with TCD is useful in ischemic disease. As discussed above, resistance arterioles supplying the brain undergo dilation in response to the hypercapnia associated with ischemia. Reactivity is a measurement of the vasodilatory response of these vessels in the presence of an exogenous stimulus, such as CO_2 or acetazolamide. This decreased response has been demonstrated in a number of studies (Kleiser et al., 1991; Ringelstein et al., 1988; Widder et al., 1994). Transcranial Doppler provides a means of evaluating reactivity that is non-invasive, portable, and time-saving. The two pages which follow show examples of a normal (Figure 1-2) and an abnormal (Figure 1-3) TCD-reactivity tracing.

Other Uses of Reactivity Studies

Reactivity in number of other settings has also been studied. These include subarachnoid hemorrhage (Dernbach et al., 1988; Hassler and Chioffi, 1989; Romner et al., 1991), migraine (Harer and von, 1991; Thie et al., 1992; Zwetsloot et al., 1991), various types of surgery (Hartl et al., 1994; Karnik et al., 1992; Lundar et al., 1985; Russell et al., 1990), head injury (Tenjin et al., 1990), and brain hemorrhage (Klingelhöfer and Sander, 1992). The specific findings of these studies are beyond the scope of this thesis.

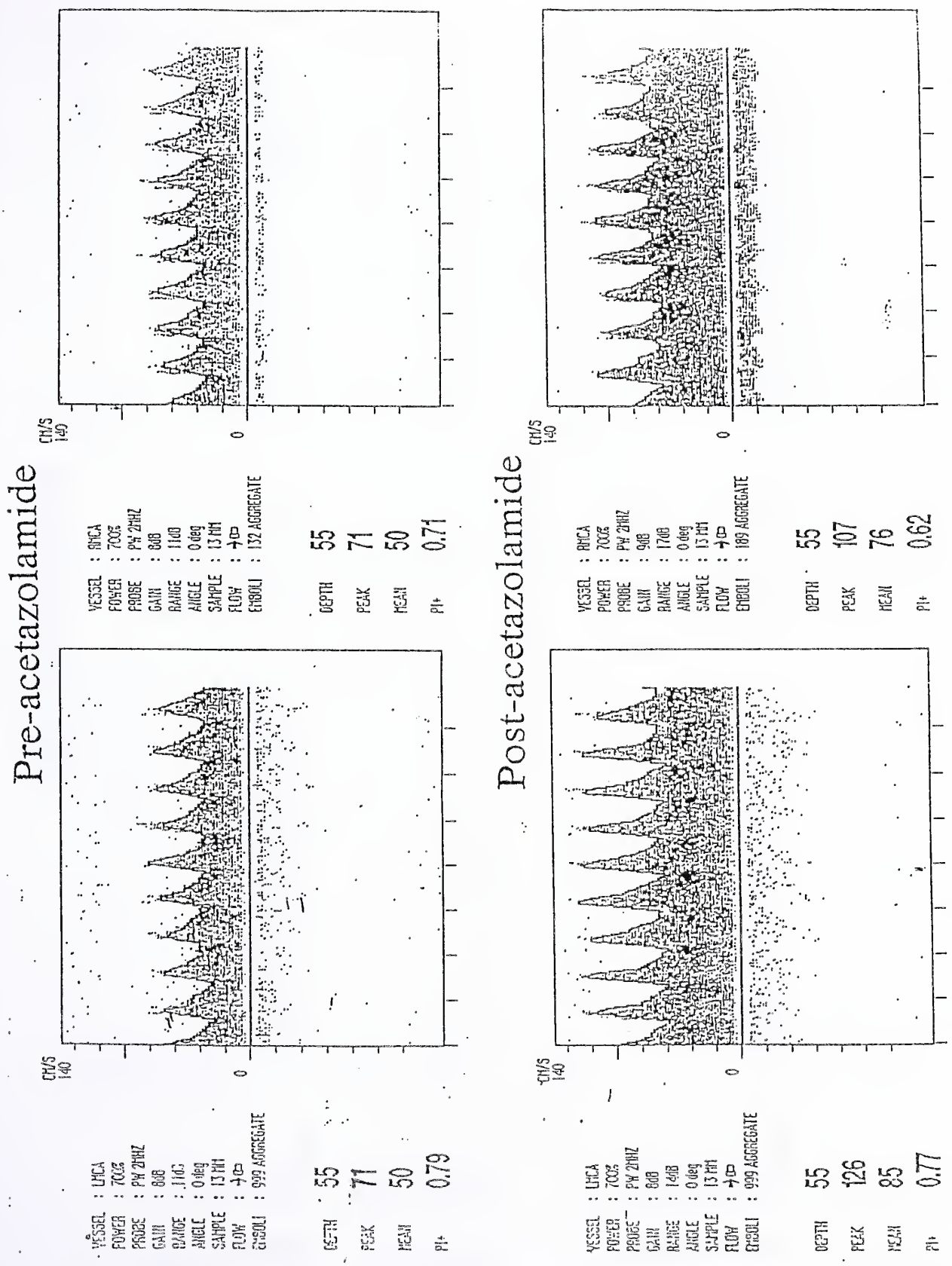

Figure 1-2. Normal TCD tracing of reactivity in a TIA patient.

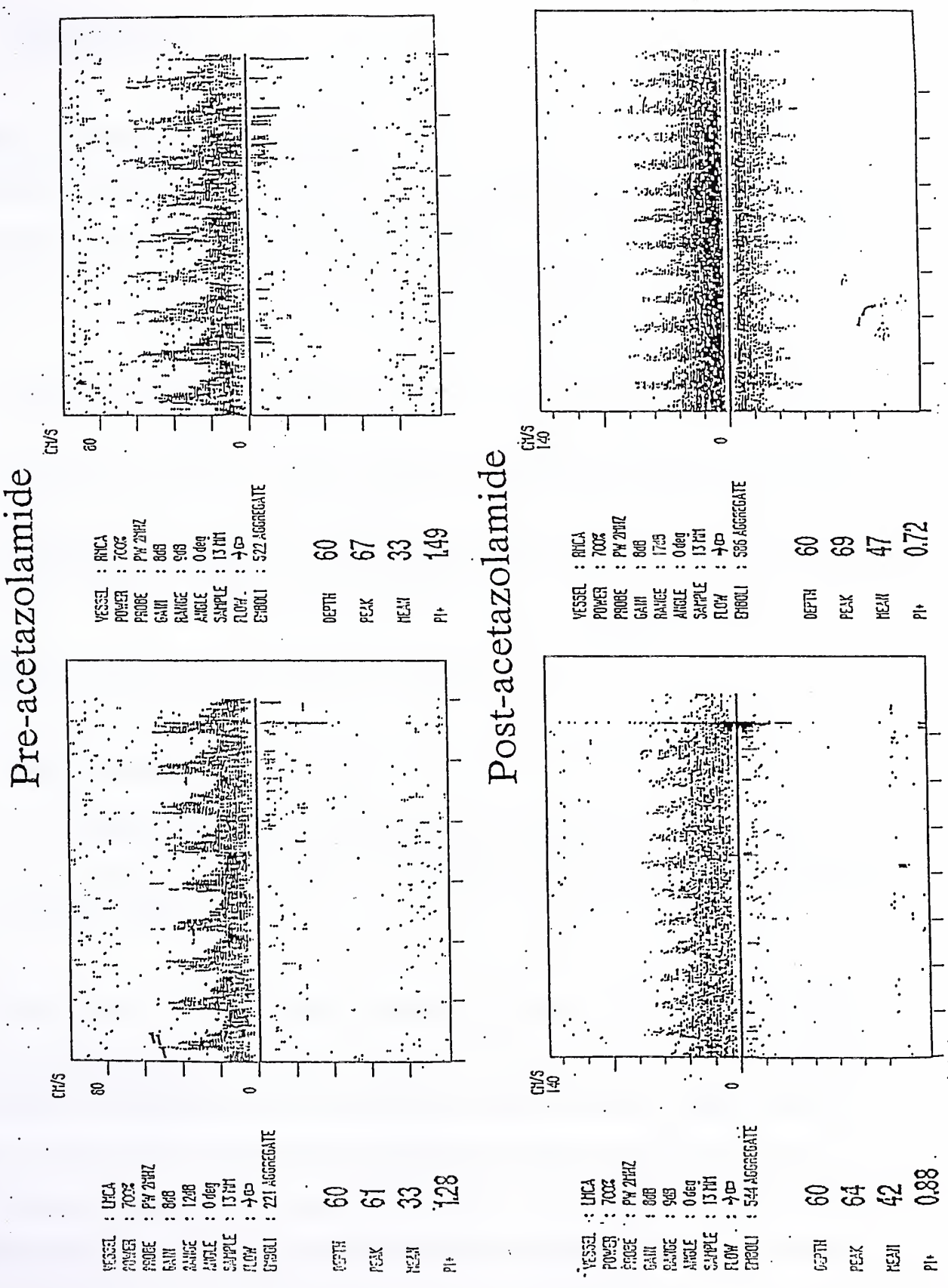

Figure 1-3. Abnormal TCD tracing of reactivity in a stroke patient.

2. Methods

Patient Identification and Acquisition

Patients for this study were identified by consulting the admission log for the Neurology service at Yale-New Haven Hospital. Those patients who met the following criteria were placed under further consideration:

- Probable stroke or transient ischemic attack by clinical history and diagnostic imaging work-up
- No other concurrent medical conditions that might confound the results of the study (e.g. Severe hypertension)
- Conditions that might be exacerbated by the use of acetazolamide (e.g. electrolyte imbalance or severe acidosis)

Exclusions were based on the following criteria:

- Equivocal clinical presentation
- Poor signals through the transtemporal bone window on either side
- The reactivity study could not be performed within seven days of the stroke or TIA

Patients who met the initial inclusion criteria underwent a routine transcranial Doppler ultrasound study. If they demonstrated acceptable transtemporal bone windows that allowed an adequate Doppler signal, they were then informed of the acetazolamide-reactivity test which would be performed as an adjunct procedure to the routine TCD study. The procedure was thoroughly explained to them, making sure they understood the purpose of the test, what to

expect during and following the tests, and the risks of the test. A procedure note and statement of verbal consent were included in the patient's chart.

Patient Demographics

A total of 61 patients (48 strokes, 13 TIAs) met the initial inclusion criteria. Of those, 32 subjects (52%) were excluded for a variety of reasons. Most of the exclusions were based on inadequate Doppler signals secondary to poor transtemporal bone windows. In addition, there was one patient with an equivocal diagnosis, and one patient whose symptoms were of psychogenic origin. The remaining exclusions consisted of patients who refused to participate in the study altogether. Finally one patient who underwent a complete acetazolamide-reactivity study had to be excluded after it was discovered that the wrong blood vessel had been insonated.

We studied 26 patients (15 men, 11 women). The mean patient age for stroke patients participating in the study was 61 years (s.d. = ±18); among TIA patients, the mean age was 56 years (±16). These patients were divided by diagnosis (based on the discharge diagnosis recorded in the medical record) and by lesion site (based on official CT and/or MRI reports). The distribution of patient diagnoses is given in table 2.1 below:

Diagnosis	Type	# of Patients	Percent
Stroke	non-lacunar	14	78%
	lacunar	4	22%
	Total	18	100%
Lesion Site	superficial	9	50%
	deep	8	44%
	combined	1	6%
	Total	18	100%
TIA	Total	8	100%
Total Patients Studied		26	

Table 2-1. Demographic information of the patients included in this study.

Transcranial Doppler Equipment

Three different transcranial Doppler (TCD) ultrasound units were used during the course of this study as the manufacturer developed updated models and software versions. The first device used was a Transpect TCD (Medasonics, Mountain View, CA). 12 patients were tested this unit.

The second unit was an updated model, the Medasonics Cerebrovascular Diagnostic System (CDS), version 1.1. Improvements were made in signal clarity, as well as hardware capabilities. 7 patients were tested using this updated device. The software for this version was updated to version 1.3.6, which further enhanced the capabilities and clarity of the machine and output. 4 patients were tested using the newer software.

The last TCD device used was the Medasonics CDS, version 2.1 Bilateral Doppler System. This updated unit permitted simultaneous bilateral testing. 6 patients were tested using the latter device.

Transducers

Ultrasound signals were generated using a 2 MHz pulsed Doppler transducer. The pulse repetition frequency is adjustable to 3.9, 5.25, 7.8, or 10.5 kHz by software under user control. The spatial peak temporal average intensity of the ultrasound is 161 mW/cm2. Since the first two models permitted only unilateral testing, two transducers were attached to a switcher box that was manually alternated between left and right during every minute of testing time.

Attachment of the Transducers

The transducers used with the first TCD unit were specially-designed so that they could be attached to a helmet that fit around the patient's head. After an adequate signal was obtained, the transducers were secured with a small screw located on either side of the helmet. The test then proceeded. Transducer placement had to be carefully monitored to avoid loss of signal if the patient suddenly moved.

The other two TCD units did not utilize a helmet. Instead, the transducers were fixed directly onto the patient either by an elastic band or with surgical cement. The elastic band was preferred, because of the extreme difficulty associated with application and removal of the cement.

Printer

Beginning with the use of the TCD unit CDS, version 1.3.6, studies were printed using a Hewlett-Packard Printrex 412 thermal printer. Recordings during the test were first stored on the hard disk and later retrieved and printed for filing.

Testing Procedure

The best transtemporal window on each side was located and the middle cerebral arteries identified first by a hand-held probe; the location was noted either by placing a pen mark or by the impression left by the conducting gel. The securable probes were then connected to the machine. For the Transpect and earliest CDS Doppler units, the two probes were connected to the switcher box then the box was connected to the machine. On the CDS Bilateral Doppler System the probes could be connected directly to the machine via two ports located in the back. Once the MCAs were re-identified, the probes could be attached as described in the section above.

Prior to the test, baseline velocities were recorded for three to five minutes; these were averaged to result in one baseline velocity for each side. Although a single recording may have been sufficient, the average of many recordings was chosen to reduce the possibility of an aberrant baseline velocity influencing the outcome of the test. When the baseline value was recorded, the patient was given 1 gram of acetazolamide (Diamox) intravenously via the cubital vein or dorsal vein of the hand, followed by a 10cc saline flush.[3] When an intravenous line or "hep-lock" line was not present, the infusion was done through a "butterfly" line.

The beginning of infusion was counted as "time zero" (T0). In order to avoid one data point greatly skewing the outcome, one reading was taken every fifteen seconds and averaged to obtain the peak (systolic) velocity for that minute. Then the unit would be switched to measure and readings for the following minute would be taken in the same manner. This method of alternate minute readings

[3]Although the preparation, set-up, and testing were all performed by NW (the principal investigator), the acetazolamide was administered by a licensed physician or certified physician's associate.

continued throughout the duration of the examination. The TCD unit, version 2.1 possessed improved insonation capabilities and accuracy, as well as the ability for taking simultaneous bilateral Doppler recordings. Therefore, use of the alternating method was no longer necessary, and only one reading per minute was required.

Timing of the Procedure

The time involved for the entire procedure was as follows: baseline = 3-5 minutes; post-acetazolamide = 25-30 minutes. The duration of baseline recordings was chosen in order to reduce the possibility of a skewed value from an aberrant data point. The duration of the test following the infusion of acetazolamide is based on previous studies which demonstrated a rise in systolic velocity during the first five minutes after giving acetazolamide followed by a plateauing of the velocity lasting approximately thirty minutes (Hague et al., 1983; Ringelstein et al., 1992). Some examinations were terminated early (i.e., after 20-25 minutes), however, if the patient became extremely tired or agitated. One patient became agitated after fifteen minutes, so the study was terminated; this did not affect the outcome, since the plateau phase had been reached. The patient suffered no other ill effects.

Recording the Studies

The Medasonics Transpect TCD and the CDS, version 1.1 units were linked to a Realistic, model 16-616 videocassette recorder and Panasonic WV-5410 monitor. Each study was recorded in its entirety and reviewed after the study to obtain individual minute readings. Appropriate labeling was done during the test so that the correct blood vessel and time could easily be identified. The updated CDS, version 1.3.6 and the CDS, version 2.1 (bilateral TCD) did not have

a video board; therefore, studies were recorded on the hard disk drive. These were retrieved in the office following the test, and the resulting images were printed out using the HP Printrex 412 thermal printer.

Data Evaluation

The raw values were entered into a Microsoft Excel spreadsheet for further calculations (a sample is provided in the Appendix section). The recorded peak (V_s) and mean (V_m) velocities, as well as the pulsatility index (PI) for each minute were entered; the spreadsheet was designed to calculate automatically the diastolic velocity using the formula for calculating the pulsatility index as defined by (Gosling and King, 1974) and solving for the diastolic velocity (V_d) as below:

$$V_d = V_s - V_m \bullet PI$$

All baseline peak velocities (V_s) and pulsatility indices (PI) were averaged to obtain one baseline value. When four values per minute were recorded, those values were averaged as the V_s and PI for that minute; when only a single value was recorded, that was used for the minute V_s and PI. Those values were further averaged to result in average post-acetazolamide velocities during the period after 7-15 minutes, 10-20 minutes and 21-30 minutes. We observed that the velocity continued to rise between T0 and seven minutes; in all patients, the increase in velocity had reached a plateau by seven minutes.

The rise in peak velocity was accompanied by a concomitant decrease in the pulsatility index. This was caused by the dilation of the resistance arterioles

distal to the MCA and served as confirmation that the vasomotor response had occurred.[4]

Cerebrovascular Reactivity: The Formula

The highest average post-acetazolamide (post-ACZ) V_s was then compared to the baseline V_s to obtain the percent cerebrovascular reactivity (CVR), using the formula below (Ringelstein et al., 1992; Sorteberg et al., 1989):

$$CVR = \%\Delta V = \left[\frac{(\text{Post-ACZ } V_s - \text{baseline } V_s)}{\text{baseline } V_s}\right] \times 100$$

A similar formula was used to obtain the percent change in the pulsatility index (PI). The ranges of the V_s were also recorded as were the % difference in V_s on the right as compared to the left. Finally a graph of each minute data point was generated by the computer. An example of this data sheet is provided in the Appendix section.

Follow-Up Studies

Follow-up acetazolamide-reactivity studies were performed on six of the 26 patients. Three patients were re-tested one week after their initial examination (i.e., approximately 14 days after their ischemic event). Three patients were re-examined during a subsequent visit to the outpatient neurology clinic. The remainder of the patients did not have follow-up studies, because of refusal to participate in the follow-up study, failure to keep their outpatient clinic

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[4]The mean velocities and pulsatility indices were not recorded in the patients tested with the Transpect TCD unit (12 patients). It was decided following this series of patients that those two parameters might be useful in data confirmation and evaluation, so they are recorded in all subsequent studies.

appointment, or because of investigator conflicts with required medical school classes.

Patient Information Database

Each patient's chart was reviewed after discharge and selected information was entered into a Double Helix database created by the principal investigator of this project. (A blank example of the information sheet is provided in the Appendix section.) The information sheet lists basic identification information about the patient, such as the name, hospital number, age, date of birth, and the attending and resident physicians who took care of that patient.

Next there is a section in which information pertaining to the study is recorded. This section includes the date of admission and discharge, the age of the patient at the time of the event as well as the estimated date of the event itself. These fields are used to calculate the number of days between the ischemic event and the reactivity study. There is also a set of fields for similar information if a follow-up study was performed. In addition, there is a field each for the admitting and discharge diagnoses; information entered here is taken from the printed discharge summary. At the end of the section there are two boxed areas in which the highest CVR for each side is recorded; there is a box for both the initial study and follow-up.

A brief medical history section is included next. Information entered here comes directly from the admission history and physical written by the neurology resident. There are fields for the chief complaint; history of present illness; past medical history, citing specifically any history of past stroke or heart disease; past surgical history, in particular any neurological surgeries; history of smoking, alcohol, or drug abuse; family history, medications, allergies. A physical exam field is included for any physical findings pertinent to the current illness.

Finally, there is a section for course of treatment and progress, which includes the results from any diagnostic tests (e.g., duplex carotid ultrasound, MRI, CT, and angiogram).

Classification of Strokes by Type

Subjects were broadly classified by the diagnosis noted at the time of discharge (ischemic stroke or TIA)[5]. The stroke patients were subclassified into lacunar and non-lacunar strokes, based lesions found by CT or MRI; these classes were chosen in order to compare strokes of different pathogenesis and prognosis. The non-lacunar strokes were further divided into deep, superficial, and combined lesions, so that comparisons between strokes of different sizes could be made.

Statistical Calculation Software

Statistical information used in the reactivity test result sheet are created using Microsoft Excel 4.0. All other statistical information was generated using the InStat v.1 software package.

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[5] Two patients were classified based on the clinical presentation and outcome, instead of the discharge diagnosis recorded in the medical record. Thus, one patient whose discharge diagnosis was TIA, suffered a stroke (with residual deficits), and another patient whose diagnosis was stroke suffered a TIA (i.e. complete resolution of symptoms within 20 minutes of onset). A third patient who presented with TIAs and underwent reactivity testing suffered a completed stroke one week following discharge, so he was classified as a stroke patient for this study.

3. Results

Comparison of the data was made between the stroke patients and those with a TIA. Values obtained from both groups were also compared with values in normal subjects obtained from a previous study (Sorteberg et al., 1989). Comparisons of the reactivity (CVR) between the symptomatic groups were made using an unpaired Mann-Whitney test, which does not assume gaussian distribution of the data. Comparisons to normal subjects were done using an unpaired Student's *t*-test.

3.1 Comparison of Patients with Brain Ischemia

Baseline Peak Velocities

The following table shows the average baseline (pre-acetazolamide) velocities (± standard deviation) in all stroke patients and all TIA patients.

Table 3-1. Mean Baseline Systolic Velocities (cm/s)

		Ipsilateral	Contralateral
All Strokes	(n = 18)	95 (±40)	98 (±53)
Superficial	(n = 9)	105 (±52)	98 (±67)
Deep	(n = 8)	85 (±25)	101 (±43)
Combined	(n = 1)	91 (0)	96 (0)
Lacunar	(n = 4)	73 (±17)	76 (±18)
Non-lacunar	(n = 14)	102 (±43)	105 (±59)
TIA	(n = 8)	88 (±20)	89 (±25)

The baseline systolic velocities were significantly higher for both stroke and TIA patients ($p < 0.01$) than velocities expected in normal subjects ($V_s = 65$ cm/s ± 6) (Sorteberg et al., 1989).

Post-acetazolamide Peak Velocities

The following table shows the average post-acetazolamide (post-acetazolamide) velocities (± standard deviation) in all stroke patients and all TIA patients.

Table 3-2. Post-acetazolamide Peak Velocities (cm/s)

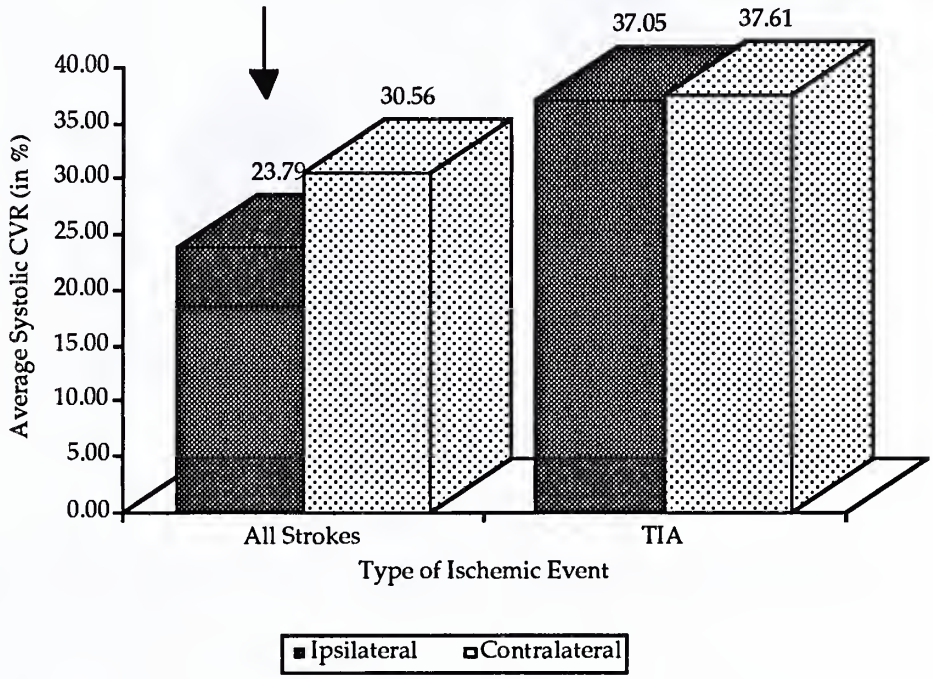
		Ipsilateral	Contralateral
All Strokes	(n = 18)	117 (±44)	128 (±66)
Superficial	(n = 9)	124 (±55)	127 (±84)
Deep	(n = 8)	111 (±35)	133 (±49)
Combined	(n = 1)	99 (0)	98 (0)
Lacunar	(n = 4)	96 (±29)	100 (±31)
Non-lacunar	(n = 14)	122 (±47)	136 (±72)
TIA	(n = 8)	120 (±25)	123 (±34)

The baseline systolic velocities were significantly higher for both stroke patients ($p = 0.01$) and TIA patients ($p = 0.02$) than velocities expected in normal subjects ($V_s = 88 \pm 6$ cm/s) (Sorteberg et al., 1989).

All Stroke Patients versus All TIA Patients

Stroke patients (n = 18), regardless of the type or location of the lesion, demonstrated an ipsilateral CVR (±s.d) = 23.79% (±12.19) and a contralateral CVR = 30.56% (±12.22). TIA patients (n = 8) demonstrated an ipsilateral CVR = 37.05%

(±10.43) and a contralateral CVR = 37.61% (±11.27). CVR on the affected (ipsilateral) side was significantly lower (p = 0.02) in stroke patients than in TIA patients. The unaffected (contralateral) side did not show a significant difference (p = 0.11).

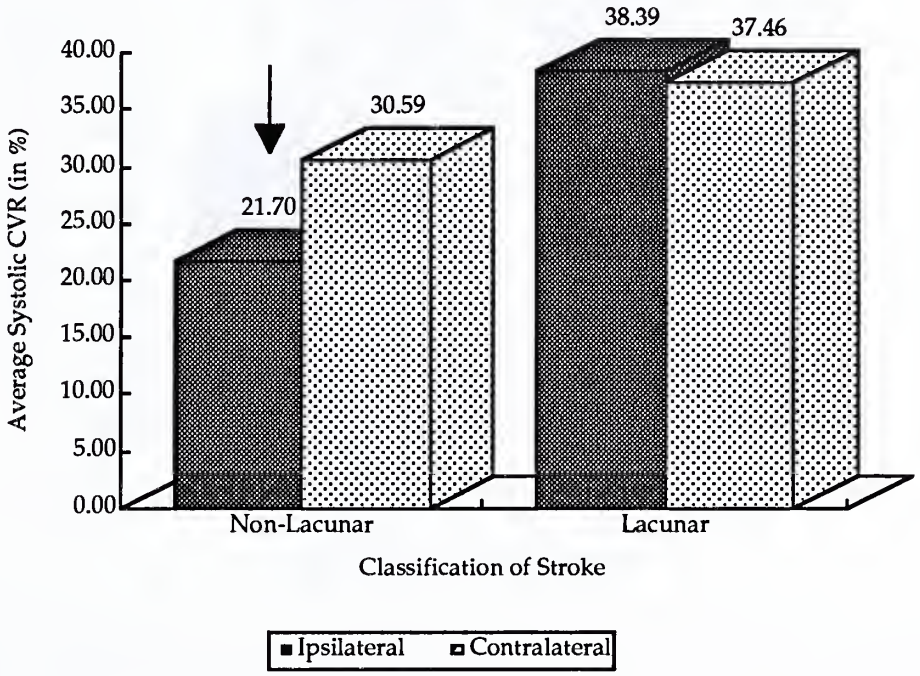


Graph 3-1. Comparison of CVR between all stroke patients and those with TIA for brain hemispheres ipsilateral and contralateral to the side of ischemic event.

Lacunar Infarcts versus Non-lacunar Infarcts

Patients with non-lacunar infarcts (n = 14) showed CVR (±s.d.) = 21.70% (±11.05) ipsilaterally and CVR = 30.59% (±12.18) contralaterally. Patients with lacunar infarcts (n = 3) showed CVR = 38.39% (±3.58) on the ipsilateral side and CVR = 37.46% (±3.52) contralaterally. Ipsilateral CVR in patients with non-

lacunar infarcts was significantly lower (p = 0.02) than in patients with lacunar infarcts. Contralateral CVR was not significant (p = 0.10).[6]



Graph 3-2. Comparison of CVR in lacunar and non-lacunar strokes.

Superficial Infarcts versus Deep Infarcts

Patients demonstrating superficial (cortical) infarcts (n = 9) demonstrated a mean ipsilateral CVR (±s.d.) = 20.21% (±11.90) and contralateral CVR = 31.32% (±13.36). Patients with deep (subcortical) infarcts (n = 8) showed a mean ipsilateral CVR = 29.67% (±10.53) and mean contralateral CVR = 33.28% (±5.81). Patients with superficial lesions showed significantly lower CVR (p = 0.05) than patients with deep (sub-cortical) infarcts. Contralateral CVR was not significant (0.48).

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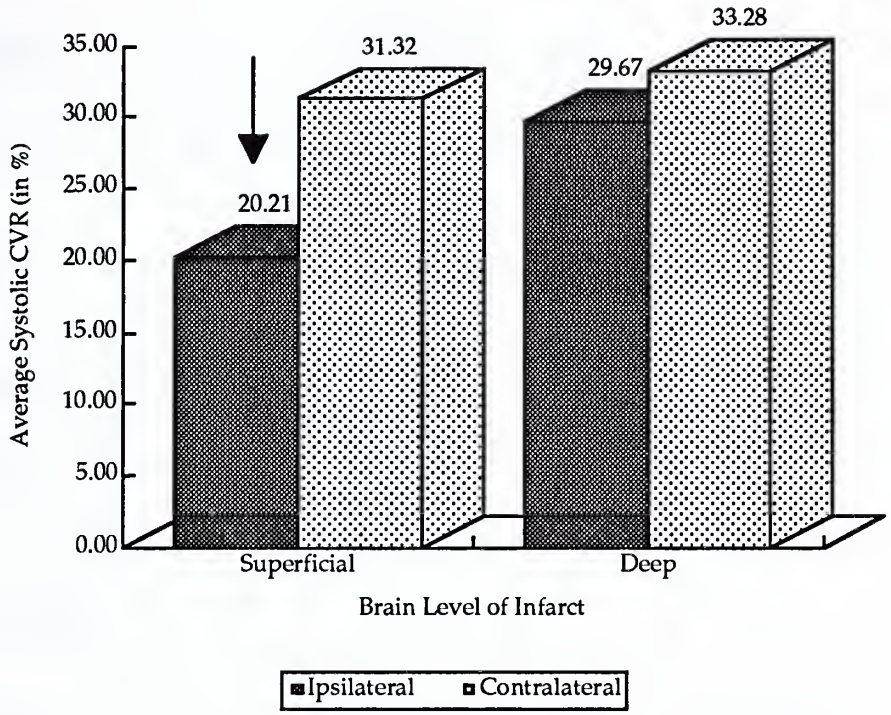
[6] One lacunar infarct data point was excluded, because it was considered an outlying point. Inclusion of this data point made the comparison of lacunar and non-lacunar infarcts slightly not significant on the affected side.



Graph 3-3. Comparison of CVR in patients with superficial and deep lesions.

Patients with Combined Deep and Superficial Lesions

Given the small sample size (n = 1), proper statistical comparisons could not be performed. However, this patient demonstrated one of the lowest CVRs of all the groups: Ipsilateral CVR = 8.85% and contralateral CVR = 2.07%.

3.2 Comparison of Reactivities in Affected Patients to Previously Studied Normal Subjects

The following results are comparisons of the patients tested for this study with normal subjects tested in a previous study (Sorteberg et al., 1989). The cerebrovascular reactivity (± standard deviation) demonstrated in normals was 36 ± 9%; this value was used to generate the statistical information given below. All comparisons were made using an unpaired, two-tailed Student's t-test.

All Stroke Patients

Side of lesion	n	Mean (%)	± s.d.	p-Value
Ipsilateral	18	23.79	12.19	< 0.01
Contralateral	18	30.56	12.22	0.08

TIA Patients

Side of lesion	n	Mean (%)	± s.d.	p-Value
Ipsilateral	8	37.05	10.43	0.78
Contralateral	8	37.61	11.27	0.70

Lacunar Strokes

Side of lesion	n	Mean (%)	± s.d.	p-Value
Ipsilateral	4	31.10	14.87	0.56
Contralateral	4	30.47	14.26	0.49

Non-lacunar Strokes

Side of lesion	n	Mean (%)	± s.d.	p-Value
Ipsilateral	14	21.70	11.05	< 0.01
Contralateral	14	30.59	12.18	0.12

Strokes with Superficial Lesions

Side of lesion	n	Mean (%)	± s.d.	p-Value
Ipsilateral	9	20.21	11.90	< 0.01
Contralateral	9	31.32	13.36	0.32

Strokes with Deep Lesions

Side of lesion	n	Mean (%)	± s.d.	p-Value
Ipsilateral	8	29.67	10.53	0.13
Contralateral	8	33.28	33.28	0.23

4. Discussion & Conclusion

4.1 Discussion of the Findings

These findings are consistent with the expectation that vasoreactivity is impaired in acute ischemic brain disease. What has been seen, however, is that this impairment is most pronounced in the setting of occlusive disease of thromboembolic nature, and in cases where there is permanent ischemic damage. Strokes that occurred secondary to small vessel disease (lacunar strokes) demonstrated less of a reactivity impairment, if any at all. Finally, vascular lesions that affected cortical regions demonstrated worse reactivity than those affecting sub-cortical regions. These differences are discussed below.

4.1.1 Stroke and TIA

It has been well documented in the literature that stroke patients demonstrate worse cerebrovascular reactivity that normal patients; TIA patients have not been extensively studied, however. The findings here show that, indeed, reactivity in stroke patients is significantly impaired, which is consistent with the principle that the resistance arterioles distal to the vessel in question—in this case the MCA—are maximally dilated and do not respond to an acetazolamide challenge.

Patients with TIA, on the other hand, tend to show higher reactivity (i.e., less impaired) values than stroke patients. Many of these numbers are within the normal range, although many are slightly impaired. Thromboembolic and occlusive disease seem to be major factors in determining the degree to which reactivity is impaired; patients who experience transient ischemic attacks demonstrate a wide variety of responses, but the fact that their disease is not yet severe enough to produce a complete infarct may account for the vasomotor

reserve capacity to be left largely intact. Impaired reactivity seen in TIA patients may have some prognostic value, suggesting that further investigation into the patency of cerebral blood supply may prevent a stroke from occurring.

4.1.2 Lacunar and Non-lacunar Infarcts

Lacunar strokes result from small vessel disease, whereas non-lacunar strokes occur because of an embolus or pre-existing occlusive disease of the blood vessels. The artery affected in a lacunar stroke is, therefore, a small branch of a larger vessel, whereas in a non-lacunar stroke, occlusion of a larger artery creates a loss in blood flow for all the blood vessels fed by it. Since most of the resistance arterioles distal to the MCA would be unaffected in a lacunar stroke, they are probably not maximally dilated. That would explain why the patients with lacunar stroke exhibit reactivity similar to that of normal persons.

4.1.3 Superficial, Deep and Combined Lesions

The superficial lesions are caused by processes affecting the larger arteries, such as the MCA, so that an occlusion would result in its resistance arterioles being maximally dilated. Disease in a branch of the larger vessels (e.g. penetrating branches of the MCA) would not cause a large degree of compensatory vasodilation, so little change in CVR should be seen when looking at the MCA, as is seen in these findings. It is likely, however, that if the branch vessels were tested, a marked decrease in their reactivity would be seen. Finally, the combined lesions represent the largest extent of disease (involvement of cortical and non-cortical structures). Although statistical analysis was not possible with only one subject, the patient demonstrated extremely impaired reactivity. A lesion located in a very proximal segment of the MCA would account for such a large stroke and for such poor reactivity.

These findings suggest that increasingly poor reactivity may be associated with increasingly larger lesions.

4.2 Some Limitations of this Study

This study looked only at the reactivity of the middle cerebral artery (MCA). What was found that only ischemic strokes that affect the MCA territory demonstrate markedly impaired reactivity, and that strokes caused by vascular changes (lacunar strokes) or those affecting other territories may not show impaired reactivity in the MCA. Further studies that would be helpful in investigating the changes in stroke include looking at the reactivity of other vascular territories (e.g. vertebrobasilar system, posterior cerebral artery, anterior cerebral artery). Comparisons could be made after strokes affecting tissues supplied by these arteries, as well as strokes affecting the other territories.

4.3 Implications of the Findings

What implications do these findings have in understanding some of the pathophysiology of stroke, and how will this knowledge affect the management of acute stroke? The management of acute stroke focuses largely on the re-establishment of tissue perfusion through anticoagulation and thrombolysis as well as strict blood pressure control. With the loss of the brain's autoregulatory capacity following a stroke, keeping blood pressure slightly elevated and avoiding, in particular, the lowering of blood pressure may play a key role improving tissue perfusion. Close monitoring of the autoregulatory capacity can be achieved by following the cerebral vasoreactivity. As the brain's autoregulatory ability returns, and reactivity improves, less strict control on blood pressure may be possible.

4.4 Future Directions and Questions

A number of further investigations should be considered, in light of the findings presented here.

1. A look at the reactivity in other vascular territories in order to better understand the characteristics of vasomotor reserve capacity.

2. Successive reactivity studies conducted in a series of patients to determine any significant improvements in reactivity over time.

3. An unpaired, prospective study comparing stroke patients who receive standard therapy and those in whom reactivity is used to guide blood pressure control.

4.5 Concluding Remarks

The intent of this research project was to compare vasomotor reactivity in a group of patients with cerebrovascular disease. While there is a great deal of knowledge that lies ahead, this study has added to scientific knowledge of one of the processes of brain function. Further understanding through investigation will have a positive impact on how patients with cerebrovascular disease are managed in the future.

5. Appendix: Data Collection Materials

The pages which follow contain examples of the materials where data were recorded.

5.1 Reactivity Test Result Sheet

YALE SCHOOL OF MEDICINE
DEPT OF NEUROLOGY

TCD REACTIVITY STUDY

PATIENT:

MINUTE DATA POINTS

TIME	LEFT				RIGHT			
	SYS	MEAN	PI+	DIA	SYS	MEAN	PI+	DIA
-6								
-5								
-4	71	50	0.79	32	71	50	0.71	36
-3	73	47	0.91	30	69	50	0.67	36
-2	73	50	0.83	32	71	50	0.73	35
-1	71	47	0.79	34	71	50	0.67	38
0	81	52	0.81	39	69	45	1.04	22
1	93	62	0.75	47	71	52	0.60	40
2	88	62	0.72	43	81	52	0.77	41
3	95	66	0.71	48	76	52	0.67	41
4	100	64	0.77	51	90	64	0.65	48
5	116	73	0.85	54	93	66	0.62	52
6	109	71	0.78	54	97	69	0.65	52
7	107	71	0.80	50	97	69	0.64	53
8	105	76	0.74	49	100	69	0.71	51
9	107	76	0.73	52	105	71	0.67	57
10	114	78	0.72	58	100	71	0.64	55
11	119	78	0.78	58	93	69	0.60	52
12	112	78	0.71	57	97	69	0.61	55
13	114	81	0.63	63	95	71	0.57	55
14	97	71	0.60	54	97	69	0.60	56
15	97	73	0.62	52	95	71	0.57	55
16	102	71	0.59	60	102	73	0.60	58
17								
18	112	73	0.82	52	95	71	0.58	54
19	112	76	0.67	61	93	66	0.58	55
20	126	85	0.77	61	107	76	0.62	60
21	116	76	0.80	55	102	71	0.68	54
22	119	78	0.75	61	109	76	0.67	58
23								
24	119	81	0.74	59	114	78	0.68	61
25	109	79	0.71	57	105	73	0.68	55
26								
27								
28								
29								

AVERAGE VELOCITY (cm/sec) & %CVR

	LEFT						RIGHT					
	SYS ± s.d.		DIA ± s.d.		PI+ ± s.d.		SYS ± s.d.		DIA ± s.d.		PI+ ± s.d.	
BASELINE	74	4	33	3	0.83	0.05	70	1	33	6	0.76	0.16
7-15 MINS	108	8	55	5	0.70	0.07	98	4	54	2	0.62	0.05
%CHANGE	46.34%		64.75%		-14.85%		39.13%		63.78%		-18.41%	
10-20 MINS	111	9	58	4	0.69	0.08	97	4	55	2	0.60	0.02
%CHANGE	49.73%		73.40%		-16.34%		38.75%		67.18%		-21.86%	
20-30 MINS	118	6	58	4	0.75	0.03	107	5	58	2	0.67	0.03
%CHANGE	59.62%		76.21%		-8.72%		52.99%		74.33%		-12.83%	
TOTAL PEAK	111	8	56	4	0.72	0.07	100	6	55	3	0.63	0.05
%CHANGE	50.41%		69.76%		-13.26%		42.95%		67.67%		-17.62%	

SYSTOLIC RANGES

	LEFT		RIGHT	
	MIN	MAX	MIN	MAX
BASELINE	71	81	69	71
PEAK	97	126	93	114

SIDE-TO-SIDE VARIATION

	SYS	DIA	PI+
BASELINE	8%	0%	8%
PEAK	11%	2%	14%

5.1a. Sample of a normal study.

YALE SCHOOL OF MEDICINE
DEPT OF NEUROLOGY

TCD REACTIVITY STUDY

PATIENT:

AVERAGE MINUTE VALUES

TIME	LEFT			RIGHT		
	SYS	DIA	PI+	SYS	DIA	PI+
-6	80	15	1.50			
-5				83	23	1.29
-4	79	21	1.44			
-3				85	21	1.31
-2	71	22	1.25			
-1				83	27	1.17
0	76	31	1.09			
1				85	15	1.50
2	70	28	0.97			
3				90	5	1.43
4	67	8	0.92			
5				112	15	1.28
6	82	10	1.66			
7				132	34	1.14
8	72	24	0.97			
9				128	41	1.15
10	71	25	1.08			
11				129	41	1.13
12	74	19	1.12			
13				122	60	0.76
14	77	26	0.54			
15				131	40	0.92
16	66	-1	1.71			
17				120	40	1.10
18	82	14	1.22			
19				123	44	1.07
20	87	36	0.89			
21				121	45	1.01
22	97	28	1.04			
23				123	32	1.03
24	88	34	0.99			
25				114	37	1.23
26	82	19	1.14			
27				125	22	1.25
28	88	23	0.79			
29				118	43	1.04

STATISTICAL DATA

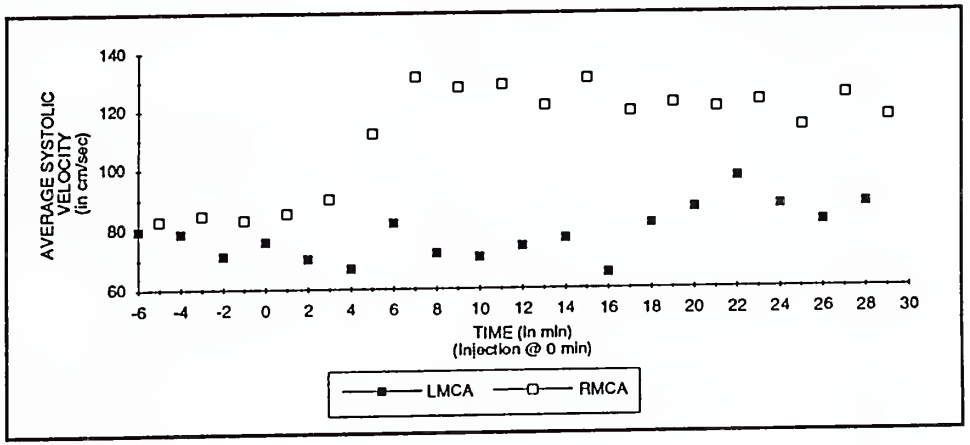
	LEFT						RIGHT					
	SYS ± s.d.		DIA ± s.d.		PI+ ± s.d.		SYS ± s.d.		DIA ± s.d.		PI+ ± s	DIA ± s
BASELINE	76	4	22	7	1.32	0.19	84	1	24	3	1.26	0.07
7-15 MINS	74	3	23	3	0.93	0.27	128	4	43	10	1.02	0.17
% CHANGE	-3.82%		4.49%		-29.52%		53.48%		81.29%		-18.89%	
10-20 MINS	76	8	20	13	1.09	0.39	125	5	45	9	1.00	0.15
% CHANGE	-0.57%		-11.70%		-17.04%		49.25%		89.56%		-20.74%	
20-30 MINS	88	5	28	13	0.97	0.14	120	4	36	9	1.11	0.12
% CHANGE	15.54%		26.94%		-26.50%		43.91%		50.15%		-11.44%	
TOTAL PEAK	80	9	22	10	1.04	0.29	124	5	40	9	1.07	0.13
% CHANGE	5.00%		0.69%		-20.74%		48.04%		67.68%		-14.94%	

SYSTOLIC RANGES

	LEFT		RIGHT	
	MIN	MAX	MIN	MAX
BASELINE	71	80	83	85
PEAK	66	97	112	132

SIDE-TO-SIDE VARIATION

	SYS	DIA	PI+
BASELINE	9%	7%	5%
PEAK	54%	77%	2%



5.1b. Sample of an abnormal study.

5.2 Patient Information Sheet

REACTIVITY PATIENT INFORMATION

INDENTIFICATION

Last	First	Unit Number
Date of Birth	Age	Attending MD
Sex		Resident MD

STUDY INFORMATION

Date of Admission
Date of Discharge
Est Age of Event
Est Date of Event
Date of Study
Days since Event

Adm Dx
Dschg Dx

Follow-up done?
Date of Follow Up
Days since Event

Initial Reactivity Results	
Left	Right
○ Low ○ High	○ Low ○ High
○ Normal ○ Abnormal	○ Normal ○ Abnormal
% CVR:	% CVR:

Follow-up Reactivity Results	
Left	Right
○ Low ○ High	○ Low ○ High
○ Normal ○ Abnormal	○ Normal ○ Abnormal
% CVR:	% CVR:

MEDICAL HISTORY

CC:

HPI:

PMH: 1. H/O CVA? Description:

2. H/O HDz? Description:

3. Other PMH: Description:

PSH: 1. Neurol Surg? Description:

2. Other Surg?

Social Hx: Smoker? Amt/length:
EtOH? Amt/fq:
Occptn
Other?

Fam Hx: 1. CVA? Who?

2. Cardiac? Who?

3. Other?

Meds:

Allergies:

PE:

Course of Treatment & Progress

5.3 Data Analysis Sheet

PATIENT DATA ANALYSIS

Name:	Unit #:	Age:
D/c dx:		

Status:
Type:
Location:
Brain level:

LICA status:
degree:

RICA status:
degree:

Initial Study	Length of time (in minutes) to absolute peak velocity:	Time range of greatest velocity percent increase from baseline:		BL	Peak	%CVR
	LMCA-	LMCA-	LMCA-			
days after event	RMCA-	RMCA-	RMCA-			

F/U Study	Length of time (in minutes) to absolute peak velocity:	Time range of greatest velocity rate of increase from baseline:		BL	Peak	%CVR
	LMCA-	LMCA-	LMCA-			
days after event	RMCA-	RMCA-	RMCA-			

IMAGING STUDIES	
Angiogram	CT/MRI

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